EXPERT OPINION

Ginger for prevention of antiretroviral-induced nausea and vomiting: a randomized clinical trial

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Objective: In this randomized clinical trial ginger efficacy for prevention of antiretroviral-induced nausea and vomiting (N/V) was investigated.

Methods: From July 2011 until the end of June 2013, 102 HIV positive patients attending the HIV clinic of Imam Khomeini Hospital participated in the study. In a double blinded manner, participants randomly received either 500 mg ginger or placebo two times per day, 30 min before each dose of antiretroviral regimen for 14 days. The severity of nausea was assessed based on the visual analogue scale. The number of vomiting episodes were also recorded during the study period.

Results: A total of 46 (90.2%) and 29 (56.4%) of the patients in placebo and ginger groups experienced some degree of nausea during the first 2 weeks of antiretroviral therapy (ART), respectively (p = 0.001). Frequency of mild, moderate and severe nausea were significantly lower in the ginger than placebo group (p = 0. 001). Also, 24 (47.1%) and 5 (9.8%) of the patients in the placebo and ginger groups reported at least one episode of vomiting during their time on ART, respectively (p = 0.01).

Conclusion: Ginger was effective in ameliorating of antiretroviral-induced N/V.

Keywords: antiretroviral, ginger, nausea, vomiting

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1. Introduction

Nausea and vomiting (N/V) are common side effects of antiretroviral therapy (ART) and usually occur early during the treatment course of HIV. Although these gastrointestinal adverse effects are usually self-limiting and disappear with continuing ART, they can affect patients' ART adherence [1,2]. Approximately 42 – 57% and 28 – 32% of patients receiving ART experience some degree of N/V, respectively [3]. Nucleoside reverse transcriptase inhibitors (especially zidovudine and didanosine), protease inhibitors (PIs) (including indinavir) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) can induce N/V [1,2]. More than two-third of people who received initial regimen from older antiretroviral drugs experienced significant adverse effects, including N/V [4]. However, with newer classes of ART including entry inhibitors, these complaints are less common [5].

In the severe forms of ART-induced N/V, discounting offending drug or switching to alternative drug may be considered. In the mild-to-moderate N/V, supportive and pharmacological approaches may be effective. Antiemetic agents including those with a combined dopamine antagonist, 5-hydroxytryptamine (5-HT) 3 antagonist and 5-HT4 agonist activity (metoclopramide), serotonin 5-HT3 receptor antagonists (ondansetron and granisetron), phenothiazines (promethazine and chlorpromazine),

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antihistamines, anticholinergics, butyrophenones, cannabinoids (dronabinol) and corticosteroids are used as antiemetic agents [3,6]. Significant adverse effects, drug–drug interactions and the cost of these medications are important issues. An effective natural product with limited drug interactions, defined safety profile and low cost is promising.

Powdered rhizome of ginger (*Zingiber officinale*) as a botanical remedy is used for alleviating N/V in several conditions [7,8]. Antioxidant, antimicrobial, antifungal, antineoplastic, antithrombotic, antidiabetic, antihyperlipidemic and antihypertensive effects have been reported for ginger [7,8]. Adverse effects related to ginger including heartburn, diarrhea and mouth irritation are mild and uncommon [9,10]. However, ginger has showed inhibitory effect on CYP enzyme activity and this should be considered when administered concomitantly with PIs specially ritronavir [11]. The main active constituents of ginger are gingerol shogaol [12]. The exact antiemetic mechanism of gingerol is unknown. Inhibition of cholinergic M3 and serotonergic 5-HT3 and 5-HT4 receptors, dopamine, substance P and NK1 receptors at the peripheral and central levels are the proposed mechanisms [12-15]. Ginger showed positive effects in controlling pregnancy-induced N/V [16,17]. It has also showed beneficial effects in the prevention and treatment of postoperative nausea and vomiting (PONV) and chemotherapy-induced nausea and vomiting (CINV) [7,18-20]. Based on the available evidence, it seems that ginger may be an effective, safe and inexpensive option for prevention of ART-induced N/V. In this randomized clinical trial for the first time, the efficacy of ginger for the prevention of ART-induced N/V was evaluated.

2. Method

2.1 Type of study and setting

This double-blind, placebo-controlled, randomized clinical trial was conducted in the HIV clinic of Imam Khomeini Hospital, a referral teaching hospital affiliated to Tehran University of Medical Sciences, Tehran, Iran, from July 2011 up to the end of June 2013. This clinic is responsible to provide free-charge patient's care (diagnostic, treatment and consultation) for the refereed HIV-positive individuals from all areas of Tehran province. Up to starting time of the study, about 1200 HIV-positive individuals registered in this clinic. Management of the HIV-positive individuals in the clinic is based on the local Iranian HIV/AIDS guideline. According to this guideline, efavirenz plus lamivudine and zidovudine is the first-line ART regimen. Lopinavir/ritonavir and didanosine are alternative medications.

The Institutional Review Board and the Medical Ethics Committee of the hospital approved the study. The study is in accordance with the Helsinki Declaration. Informed consent was obtained from all patients or their family members. The trial was registered in the Iranian Registry of Clinical Trial with ID number IRCT201305283449N12.

2.2 Patients

Sample size of the study was calculated based on the data of previous study (3), $\alpha = 0.05$ and 80% power ($1\text{-}\beta = 0.8$). During the study period, 176 HIV-positive patients were eligible for initiating ART. Following initial interview, only 137 adult patients (18 – 65 years old) agreed to participate in the study and signed the consent form. In the second phase of interview, patients with underlying gastrointestinal disorders (current and history of peptic ulcers, dyspepsia, N/V, using antiemetic and antiacid products), noncompliance, positive history for ginger hypersensitivity and concomitant anticoagulant therapy were excluded. A total of 115 patients were initially included, with 102 patients completing the study (**Figure 1**). Following patients' medical records review, the patients' demographic and clinical data were recorded. The included patients were assigned to either the ginger or placebo group based on simple randomization. Capsules of ginger were provided from the GOLDAROO pharmaceutical company, Isfahan, Iran. Ginger capsules are available as a herbal product in the Iranian pharmaceutical market and each capsule contained 250 mg standard powdered rhizome of ginger. Periodical analysis and quality control of the product is carried out by the company under supervision of the standard Drug and Food Control Laboratory affiliated to the Ministry of Health, Tehran, Iran. Placebo capsules filled with starch were the same shape and provided in the same packaging to the ginger capsule. They were manufactured by the same pharmaceutical company.

Each included patient referred to pharmacy department of the HIV/AIDS clinic was divided by the simple randomization method into the ginger or placebo group by a pharmacy technician. The main researcher (clinical pharmacist) and patients were blinded regarding the type of capsules. Participants received either two capsules of ginger (500 mg) or placebo, two times per day, which was taken 30 min before each dose of ART for 14 days. All included patients were educated regarding gastrointestinal adverse effects of ART and asked to avoid any medication for controlling gastrointestinal problems including N/V. Any patient who needed antiemetics, antiacids, nonadherent with ART regimens or cessation of ART for controlling ART-induced gastrointestinal problems was withdrawn from the study.

An expert clinical pharmacist in the field of infectious diseases was responsible for education of the patients regarding gastrointestinal adverse effects of ART, N/V assessment and patient follow-up by phone and at visit times. All patients were advised regarding their use of ART regimen and were asked not to change their meal regimens during the study period. Severity of nausea was assessed based on the visual analogue scale (VAS); an instrument for subjective characteristics or attitudes that cannot be directly measured. A standard VAS was used that point 0 equals to the absence of nausea and point 10 was taken into account as the most severe condition of nausea. Scores ≤ 3, 4 – 7 and > 7 were considered as mild,

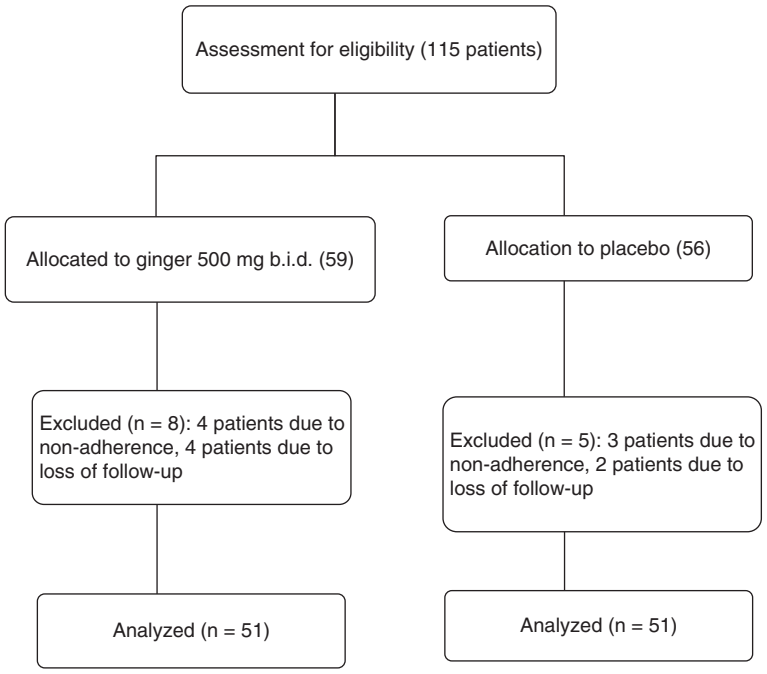

Figure 1. Consort flowchart of the study.
b.i.d.:Two times a day.

moderate and severe nausea, respectively. The validity of the VAS was evaluated by an expert clinical pharmacist. Internal consistency reliability was evaluated by the finding the Cronbach's α-coefficient for all items on a 20 randomly selected non-HIV-infected patients involved with N/V. Test–retest reliability was assessed by finding the intra-cluster correlation on the same sample after a week. According to the findings, content modification of the VAS was applied and its finalized format was employed. Initially, patients were educated regarding this scale and a copy of the scale was given to each patient. The patients were monitored daily via phone calls during which they were asked about their adherence to treatment regimens and gastrointestinal adverse effects (including N/V) during the first 14 days of therapy by a clinical pharmacist. At two clinic visits at the beginning and the end of follow-up as well as during daily phone calls, patients were asked to report any episode of gastrointestinal adverse reaction including N/V. The clinical pharmacist asked patients who experienced nausea to determine the severity of each episode of nausea based on the in-hand VAS scale.

2.3 Statistical analyses

The statistical package of social science version 11.5 was used for all analyses. Means ± standard deviations (SDs) were calculated for continuous variables and percentage for categorical variables. All data were examined for normal distribution by the Kolmogorov–Smirnov test. The χ^2 (or Fisher's exact test) was used to compare categorical demographic and clinical data of patients. The Mann–Whitney U test was used to compare non-normally distributed continuous variables. We considered $p < 0.05$ as statistically significant.

3. Results

A total of 102 patients completed the study. Among these, 70 (68.6%) and 32 (31.4%) were male and female, respectively. Mean ± SD age of the cohort was 35.89 ± 9.19 years. NNRTIs-based regimen (efavirenz + lamivudine + zidovudine) was the most common (97.0%) ART protocol. The most frequent opportunistic infection in our patients was candidiasis (9.80%). The most common (76.99%) indication for starting ART in the subjects was CD4 < 350 cells/ml. The major route of HIV transmission was intravenous drug use (59.80%). Demographic characteristics and laboratory data of the patients are shown in **Tables 1** and **2**. There was no statistically significant difference between the ginger and control groups regarding baseline characteristics and laboratory data ($p > 0.05$).

A total of 46 (90.2%) and 29 (56.9%) patients in the placebo and ginger groups experienced some degree of nausea during the first two weeks of ART, respectively ($p = 0.001$) (**Table 3**). In total, 273 and 175 episodes of nausea were recorded in the placebo and ginger groups, respectively (**Table 4**). Frequency of mild, moderate and severe episodes of nausea was significantly lower in the ginger group than in the placebo group ($p = 0.02$, 0.04 and 0.001, respectively) (**Table 4**). Also, 24 (47.1%) and 5 (9.8%) patients in the placebo and ginger groups reported at least one episode of vomiting, respectively ($p = 0.01$) (**Table 5**).

Table 1. The demographic characteristics of the patients.

Characteristics		Ginger group (51 patients)	Placebo group (51 patients)	*p value
		Number (%) or mean ± SD	Number (%) or mean ± SD	
Sex	Male	36 (70.58)	34 (66.66)	0.41
	Female	15 (29.42)	17 (33.34)	
Age		36.82 ± 9.29	34.7 ± 9.03	0.40
Time interval from HIV infection to reaching AIDS stage (months)		18.22 ± 21.13	15.95 ± 11.34	0.22
Education	Illiterate	4 (7.84)	3 (5.88)	0.11
	Elementary	3 (5.88)	6 (11.76)	
	Guidance school	16 (31.37)	14 (27.45)	
	High school	22 (43.13)	25 (49.01)	
	More than diploma	6 (11.76)	3 (5.88)	
Transmission routes	IV drug injection	32 (62.74)	29 (56.86)	0.56
	Sexual contact	11 (21.56)	10 (19.60)	
	Both IV drug injection and sexual contact	4 (7.84)	8 (15.68)	
	Unknown	2 (3.92)	2 (3.92)	
	Blood product transfusion	2 (3.92)	2 (3.92)	
Opportunistic infections	TB	2 (3.92)	1 (1.96)	0.11
	CMV	1 (1.96)	2 (3.92)	
	Candidiasis	3 (5.88)	2 (3.92)	
	Zoster	2 (3.92)	0 (0.0%)	
	Candidiasis	3 (3.58)	1 (1.96)	
	None	40 (78.43)	45 (88.23)	
Concomitant diseases	Diabetes	2 (3.92)	1 (1.96)	0.87
	Depression	3 (5.88)	4 (7.84)	
	HCV	10 (19.60)	8 (15.68)	
	HBV and HCV	6 (11.76)	4 (7.84)	
	None	30 (58.82)	34 (66.66)	
Stage of HIV infection	A	31 (60.78)	36 (70.58)	0.32
	B	13 (25.49)	8 (15.68)	
	C	7 (13.72)	7 (13.72)	
Concomitant medications	Cotrimaxazole	23 (45.09)	25 (49.01)	0.22
	Gancyclovir	2 (3.92)	1 (1.96)	
	Benzodiazepine	4 (7.84)	2 (3.92)	
	SSRI	6 (11.76)	8 (15.68)	
	Fluconazole	4 (7.84)	4 (7.84)	
	INH	5 (9.80)	5 (9.80)	
	Anti-TB regimen (INH, RIF, PYZ, ETM + Vit B6)	1 (1.96)	1 (1.96)	
	Acyclovir	3 (5.88)	1 (1.96)	
	Insulin	3 (5.88)	4 (7.84)	
ART regimens	Efavirenz + lamivudine + zidovudine	42 (82.35)	44 (86.27)	0.10
	Lopinavir/ritonavir + lamivudine + zidovudine	7 (13.72)	6 (11.76)	
	Lamivudine + zidovudine + didanosine	2 (3.92)	1 (1.96)	

*χ^2 or Fisher's exact test.

ART: Antiretroviral therapy; B6: Vitamin B6; ETM: Ethambutol; HBV: Hepatitis B Virus; HCV: Hepatitis C virus; INH: Isoniazid; i.v.: Intravenous; NS: Not significant; PYZ: Pyrazinamide; RIF: Rifampin; SSRI: Selective serotonin reuptake inhibitor; TB: Tuberculosis.

4. Discussion

Gastrointestinal complications including N/V are common complaints of patients following initiating of ART regimens. Most antiretroviral drugs cause transient N/V at the beginning of therapy course. These adverse effects can result in discontinuation of ART and patient nonadherence [1-3]. Mild N/V is usually self-limiting, but for moderate-to-severe cases, antiemetic medications may be helpful. Dopamine and serotonin antagonists, phenothiazines, antihistamines,

Table 2. Patients' laboratory data.

Variable (mean ± SD)	Ginger group (51 patients)	Placebo group (51 patients)	*p value
WBC	4920.23 ± 1003.22	5661.23 ± 1994.8	0.11
CD4 count	238.23 ± 100.67	198.67 ± 150.99	0.45
Hemoglobin	11.22 ± 2.49	10.68 ± 1.84	0.89
Hematocrit	34.11 ± 4.67	33.99 ± 5.84	0.65
Platelets	195317.44 ± 104829.60	206441.52 ± 173125.22	0.54
Urea	22.00 ± 7.64	25.00 ± 10.19	0.44
Creatinine	1.05 ± 1.39	0.96 ± 0.21	0.23
ALT	58.91 ± 23.81	67.31 ± 24.14	0.45
AST	50.74 ± 67.16	56.86 ± 11.00	0.76
ALP	373.09 ± 42.45	287.18 ± 26.14	0.54
ESR	22.13 ± 9.11	25.31 ± 11.40	0.55
Cholesterol	129.32 ± 30.13	150.06 ± 31.50	0.09
Triglyceride	141.89 ± 43.20	182.11 ± 58.26	0.33
HDL	36.16 ± 12.10	30.11 ± 9.50	0.54
LDL	89.10 ± 23.10	96.11 ± 27.01	0.45
FBS	112.48 ± 24.49	122.60 ± 68.26	0.77

*Two tailed t test.

ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ESR: Erythrocyte sedimentation rate; FBS: Fasting blood sugar; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; SD: Standard deviation; WBC: White blood cell.

Table 3. Number (%) of patients with and without nausea.

Treatment group	Without nausea, n (%)	With mild nausea, n (%)	With moderate nausea, n (%)	With severe nausea, n (%)	Total patients with nausea, n (%)
Ginger	22 (43.1)	9 (17.6)	16 (31.4)	4 (7.9)	29 (56.9)
Placebo	5 (9.8)	14 (27.4)	20 (39.2)	12 (23.6)	46 (90.2)
p* Value	0.001	0.02	0.04	0.001	< 0.001

*χ^2 test.

%: Percent of patients; n: Number of patients.

Table 4. Frequencies of nausea episodes and different intensities during first two weeks of ART.

Treatment group	Mild nausea, n (%)	Moderate nausea, n (%)	Severe nausea, n (%)	Total frequency, n (%)
Ginger	63 (36.0)	84 (48.0)	28 (16.0)	175 (100)
Placebo	98 (35.9)	112 (41.0)	63 (23.1)	273 (100)
p Value				< 0.001

*χ^2 test.

%: Percent of patients; ART: Antiretroviral therapy; n: Number of patients.

Table 5. Number (%) of patients with and without vomiting.

Treatment group	Patients without vomiting, n (%)	Patients with one episode of vomiting, n (%)	Patients with two episodes of vomiting, n (%)	Patients with 3 – 6 episodes of vomiting, n (%)	Patients with more than six episodes of vomiting, n (%)	Total patients with vomiting, n (%)
Ginger	46 (90.2)	2 (3.9)	2 (3.9)	1 (2)	0 (0)	5 (9.8)
Placebo	27 (52.9)	12 (23.5)	5 (9.8)	4 (7.8)	3 (6)	24 (47.1)
p* Value	0.01	0.006	0.04	0.03	0.02	< 0.001

*χ^2 test.

%: Percent of patients; n: Number of patients.

anticholinergics, butyrophenones, cannabinoids and corticosteroids are usually recommended as antiemetic medications. Adverse effects, drug interactions and cost are challenging issues regarding antiemetic administration for the management of ART-induced N/V [3]. A drug with favorable safety profile, no significant drug interaction and low cost can be considered as a desirable option for this purpose (indication). Ginger is an ancient medicinal plant that has been used as an antiemetic. Ginger has not shown any significant drug interactions or side effects. It is inexpensive and is available around the world [8,19,20].

Effects of ginger on the prevention of pregnancy-induced N/V, PONV and CINV have been evaluated in the previous studies, but this is the first time that preventive effects of ginger against ART-induced N/V are examined. Ginger significantly reduced the incidence of ART-induced N/V in the current study. Our cohort also received a number medications (e.g., cotrimaxazole, fluconazole, benzodiazepines, selective serotonin reuptake inhibitors, isoniazid, rifampin, pyrazinamide) for either prophylaxis of opportunistic infections or management of their comorbidities (such as depression and tuberculosis) that may aggravate gastrointestinal adverse reactions of ART. However, the number of patients given these agents was comparable between placebo and ginger groups. This was also true for medications with potential therapeutic effects against N/V such as pyridoxine (vitamin B6).

Three independent study groups have investigated the effect of ginger on prevention of CINV [20-22]. The results of Sontakke *et al.* study showed that ginger is as effective as metoclopramide in reducing CINV. In that study, participants randomly received three regimens. First regimen was two capsules of ginger orally (each capsule contained 250 mg powdered ginger) and 2 ml of normal saline intravenously (i.v.) 20 min before chemotherapy and then the dose of ginger was repeated 6 h after chemotherapy. Second regimen included two capsules of lactulose orally and metoclopramide (20 mg) i.v. given to patients 20 min before chemotherapy and then they received two capsules of metoclopramide (5 mg) 6 h after chemotherapy. Third regimen was two capsules of lactulose orally and ondansetron (4 mg) i.v. 20 min before chemotherapy and then the patients received two capsules of ondansetron (4 mg) 6 h after chemotherapy [20].

Pillai *et al.* demonstrated that powdered ginger is as effective as add-on therapy to antiemetic medications for reducing CINV in children and young adults. Participants with body weight between 20 and 40 kg received 1 g/day ginger (6 capsules of 167 mg ginger) or matching placebo from day 1 to day 3 of chemotherapy. Patients with body weight between 40 and 60 kg took 2 g/day ginger (5 capsules of 400 mg ginger) or matching placebo from day 1 to day 3 of chemotherapy [21]. In another study, ginger at doses of 0.5 and 1 g per day significantly reduced CIN as add-on to standard antiemetic regimens. Patients randomly assigned into four groups and received placebo, 0.5, 1 or 1.5 g ginger per day. Three capsules (ginger extract or placebo) were given twice daily for 6 days, started 3 days before chemotherapy [22].

Bone *et al.* and Nanthakomon and Pongrojpaw evaluated the effect of ginger on the prevention of PONV [23,24]. In the Bone *et al.* study, ginger significantly reduced PONV and additional antiemetic medications were needed. The antiemetic effect of ginger was similar to metoclopramide. Patients were randomly divided into three groups. Group 1 received 1 g ginger orally and 2 ml sterile water as i.v. placebo, and group 2 received 1 g lactulose as orally placebo and 10 mg of metoclopramide as i.v. injection. One gram orally placebo and 2 ml i.v. placebo were given to group 3. Ginger or placebo capsules were administrated 1.5 h before surgery [23]. In another study by Nanthakomon and Pongrojpaw, ginger was an effective antiemetic agent for the prevention of PONV. Participants randomly received 1 g powdered ginger (500 mg per capsule) or 1 g placebo (500 mg lactulose per capsule) 1 h before surgery [24].

Nale *et al.* investigated the effect of ginger on the prevention of PONV in comparison with other antiemetic medications. They also recorded cost and side effects of the medications. Participants randomly assigned to receive one of the following six interventions: ginger 250 mg (group 1), metoclopramide 10 mg (group 2), prochlorperazine 5 mg (group 3), promethazine 20 mg (group 4), ondansetron 4 mg (group 5) or placebo (group 6) 1 h before surgical procedure and at 8 h intervals for 24 h. They concluded that ginger was a very effective intervention for the prevention of PONV and the severity and incidence of N/V were lowest in the ginger group than the other groups. Ginger was the most cost-effective intervention with negligible adverse effects compared with other drugs [25]. A meta-analysis by Chaiyakunapruk *et al.* concluded that ginger is an effective antiemetic to prevent PONV. Ginger can be used as at least an add-on therapy to antiemetic regimen for controlling PONV due to its availability, being inexpensive and desirable safety profile [26].

In the present study, frequency of both N/V episodes significantly decreased in the ginger group, but ginger was more efficacious against vomiting compared with nausea. This concept that antiemetics are more efficacious against vomiting than nausea was reviewed recently by Andrews and Sanger [27].

ART-induced gastrointestinal adverse reactions including nausea, vomiting and dyspepsia are the most frequently reported side effects of ART regimens [28]. Gastrointestinal intolerance was the main cause of lopinavir/ritonavir therapy modification or interruption, whereas it was less commonly associated with efavirenz discontinuations [29]. The incidence of gastrointestinal adverse reactions was higher in patients treated with nelfinavir compared with nevirapine [30]. Also, these reactions were the main cause of saquinavir therapy modification. However, no patient on atazanavir/ritonavir discontinued treatment due to GI intolerance [31,32]. Gastrointestinal toxicity was also reported with didanosine. Zidovudine and

didanosine showed higher rates of nausea, constipation and fatigue compared with stavudine and lamivudine [33].

This study is the first to evaluate the antiemetic effect of ginger on ART-induced N/V. In our study, ginger was an effective intervention to prevent antiretroviral regimen-induced N/V. Patients tolerated ginger well, and no considerable adverse effects were detected. The study was limited by its small sample size. Moreover, the duration of patient follow-up may not be sufficient as gastrointestinal adverse effects of ART may occur beyond 2 weeks of therapy. Patients were followed daily through phone during the study period. This type of follow-up may affect the accuracy of results. VAS was used for the assessment of the patients' severity of nausea. Although the scale was always being used in many studies and was validated in this trial, the patients may not have adhered to the scale during the follow-up period. Further randomized clinical trials must be conducted to confirm the efficacy of ginger in the prevention of ART-induced N/V. More studies are required to determine the best dose and time of ginger administration in the prevention of ART-induced N/V.

Declaration of interest

This study was the result of a pharm.D student's thesis and was supported by the Tehran University of Medical Sciences. Clinical trial registration TRCT201305283449N12. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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